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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/828,876	04/10/2001	Steven L. Stice	P 0280088	1054

7590 11/06/2003

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/828,876	STICE ET AL.	
	Examiner	Art Unit	
	Thái-An N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *78-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78-89* is/are rejected.

7)☒ Claim(s) *78 and 85* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 8/7/03, has been entered. Claims 1-77 have been cancelled. Claims 78-89 have been added and under current examination.

Any rejection made of record in the prior Office action, mailed 11/19/02, Paper No. 7, and not made of record in the instant Office action, has been withdrawn in view of Applicants' arguments and/or amendments to the claims.

Claim Objections

Claim 78 is objected to because of the following informalities:

1) The term "unit" is misspelled in part (iii) of the claim

2) The term "unit" is misspelled in part (iv) of the claim

Claim 85 is objected to because of the following informalities: the term "hematopoietic" is misspelled.. Appropriate correction is required.

Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214

USPQ 761 (CCPA 1982); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Newly added claims 78-89 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 6,235,970 B1. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claims) because the examined claim is either anticipated by, or would have been obvious over, the reference claims). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQZd 1226 (Fed. Cir. 1998)) In re Goodman, 11 F.3d 1046, 29 USPQZd 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims encompass the subject matter of claims 1-18 of '970.

The present claims are drawn to methods of producing a CICM cell line comprising inserting a desired differentiated mammalian cell or cell nucleus into an enucleated oocyte of the same species as the mammalian cells or cell nucleus to form an NT unit, activating the NT unit, culturing the NT unit until greater than the 2-cell stage; and culturing cells obtained from the cultured NT unit to obtain a

CICM cell line. The proliferating differentiated somatic donor cell or donor cell nucleus of claims 1-18 in '970 are within the scope of differentiated mammalian cell or cell nucleus of the present claims. The greater than 2-cell stage, as in the present claims, is encompassed by the limitation in '970 of culturing until at least a size suitable for obtaining ICM cells, or culturing to form a blastocyst. The culturing step of the present claims is defined by the present specification to take place on a feeder layer with growth to at least 50 cells as claimed in claims 2, 16, and 17 of '970. The present specification defines transgenic as being any modification as claimed in claims 5-9 and 11 of '970. The term mammal in the present claims is defined by the present specification to be any one of the mammals of claims 10 and 12-14 in '970.

Note that Applicants' argue that the filing of a Terminal Disclaimer over the '970 patent obviates the prior rejection. See p. 15 of the Response. At the time of this Office action, no Terminal Disclaimer has been received; as such the prior rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 78-89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing a CICM cell line comprising inserting a desired mammalian somatic cell or mammalian somatic cell nucleus into an enucleated mammalian oocyte of the same species as the somatic cell or somatic cell nucleus, under conditions suitable for the formation of an NT unit, activating the resultant NT unit, culturing the NT unit until greater than the 2 cell developmental stage and no greater than the 400-cell developmental stage and culturing cells obtained from the cultured NT unit to obtain a CICM cell on a fibroblast feeder layer to maintain the CICM cell line in an undifferentiated state, does not reasonably provide enablement for methods of producing a CICM cell line comprising inserting a mammalian somatic cell or cell nucleus into an enucleated mammalian oocyte of the same species as the somatic cell or cell nucleus, under conditions suitable for the formation of an NT unit, activating the resultant NT unit, culturing the NT unit until greater than the 2 cell developmental stage and no greater than the 400-cell developmental stage and culturing cells obtained from the cultured NT unit to obtain a CICM cell under conditions that maintain the CICM cell line in an undifferentiated state, for reasons of record advanced on pages 3-4 of the prior Office action. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that the prior rejection is now moot because the newly added claims recite "somatic" donor cells. See pp. 15-16 of Applicants' Response.

This is not found to be persuasive. The claim specifically recites that the donor cell is a mammalian somatic cell *or cell nucleus*. See part (i) of claim 78. There is no indication that the cell nucleus would be a somatic cell nucleus. As such, it is reiterated that germ cells are encompassed by the instant claims, and that such cell nuclei are not enabled. In particular, germ cells are haploid, and it is unpredictable that the insertion into of a haploid nucleus into an enucleated oocyte would result in embryonic growth, as required for the formation of inner cell mass cells. Further, it is unpredictable that any cellular growth of a haploid cell would result in the development of inner cell mass cells, which compose an embryonic structure. There is no evidence of record or in the art that a haploid nucleus can support embryonic development to the point where inner cell mass cells form in the embryo. ICM cells, required for the present invention, are only found in later embryos, usually at the blastocyst stage. ICM cells do not exist at the early embryo stage.

Furthermore, with regard to the requirement for culturing the cells on a fibroblast feeder layers to maintain an undifferentiated state, the specification clearly teaches that, "ES cells can be passaged in an undifferentiated state, provided that a feeder layer of fibroblast cells or differentiation inhibiting source is present." See p. 1, lines 22-24. The specification further teaches that maintaining

ES cells on feeder layers prevents overt differentiation [see p. 9, lines 9-11], and that that the CICM cells of the instant invention will be plated on layers of irradiated fibroblast feeder cells. See p. 19, lines 19-30. The state of the art further supports that to maintain ES cells in an undifferentiated state, there is a fundamental requirement for feeder layers to prevent differentiation. Thomson *et al.* discuss the difficulties in culturing pPS in feeder free conditions. Thomson *et al.* (**PNAS**, 92:7844-7848, 1995) teach the derivation of a cloned cell line from a rhesus monkey that remains undifferentiated when grown on mouse embryonic fibroblast feeder layers, but differentiate or die in the absence of the fibroblasts (see p. 7844, *Abstract*). Particularly, Thomson *et al.* state that in the absence of the feeder layers, soluble human leukemia inhibitory factor (LIF) fails to prevent the differentiation of the cells, and that the factors that fibroblasts produce to prevent the differentiation of the cells is yet unknown (see p. 7847, 1st column, 2nd paragraph). Thomson *et al.* further state that human inner cell mass-derived cells were cultured in the absence of feeder layers failed to survive beyond 2 passages (see p. 7848, 1st paragraph). Accordingly, it is maintained that cells, such as the CICM cells of the instant invention would need to be cultured on a feeder layer in order to prevent differentiation, as required by the claims.

With regard to claims 85 and 86, which are directed to generating hematopoietic cells [claim 85] and neural cells from hematopoietic cells [claim 86], the specification fails to provide sufficient teachings or guidance such that one of

skill in the art would have been able to make and use the claimed invention. Particularly, the specification relies on the art to practice the claimed methods. The specification cites Palacios and Bain as support for generating hematopoietic stem cells from mouse ES cells [Palacios] and generating neural cells from mouse ES cells [Bain]. Palacios teaches that mouse ES cells were induced to differentiate into hematopoietic stem cells by co-culturing the cells with the stromal cell line RP010 and the combination of interleukins 3, 6, and F. Bain teaches the generation of neuronal-like cells by culturing mouse ES as aggregates in the presence of retinoic acid. Neither reference provides teachings, guidance, or evidence with regard to the differentiation of hematopoietic cells into neural cells, as required by the claims. Furthermore, it is noted that claim 85 broadly recites "hematopoietic cells". This includes a large number of cells, such as hematopoietic stem cells, as well as terminally differentiated cells, such as white blood cells and red blood cells. Neither the cited art of record nor the specification provides teachings or evidencewith regard to the transdifferentiation of a terminally differentiated hematopoietic cell to a neural cell.

Accordingly, it is maintained that at the time of the instant invention, it would have required the skilled artisan to engage in an undue amount of experimentation, without a predictable degree of success, to implement the present claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 78, as written, is unclear. The claim recites that the activated NT unit is cultured until greater than the 2-cell developmental *state* and no greater than the 400-cell developmental *stage*. It is unclear if it is the developmental state or stage that the claim refers to. Claims 79-89 depend from claim 78. Appropriate correction is required.

Claim 85, as written, is unclear. The claim recites the method of claim 84, which results in hematopoietic cells. However, claim 84 (which is dependent on independent claim 78) recites a method of producing a CICM cell line that maintains the CICM cell line in an undifferentiated state. As such, producing hematopoietic cells, as required by claim 85, is contrary to the method steps recited in claim 78 as claim 78 fails to recite any method steps that would result in hematopoietic (differentiated) cells. Claim 86 and 87 depend from claim 85.

Claim 86, as written, is unclear. The claim recites the method of claim 85, which results in neural cells. Claim 85, (which is dependent upon independent claim 78) recites a method of producing a CICM cell line that maintains the CICM cell line in an undifferentiated state. As such, the claim is contrary to the method steps recited in claim 78 because claim 78 fails to recite any method steps that would result in the generation of neural cells from hematopoietic cells. Claim 87 depends from claim 86.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)-872-9306.

TNT

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